II. Nonstatutory Double Patenting Rejection of Claims 1, 7 and 8

The Action first rejects claims 1, 7 and 8 under the judicially created doctrine of obviousness-type double patenting, as allegedly being unpatentable over claims 1, 4 and 6 of U.S. Patent No. 6,777,232. In order to overcome the present nonstatutory double patenting rejection, Applicants submit herewith a Terminal Disclaimer with regard to U.S. Patent No. 6,777,232.

Applicants submit that the nonstatutory double patenting rejection has been overcome, and respectfully request withdrawal of the rejection.

III. Rejection of Claims 1, 7 and 8 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 7 and 8 under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention comprising a genus of at least 80 contiguous nucleotides of SEQ ID NO:9. Applicants respectfully traverse.

The Action states that claims 1, 7 and 8 are not enabled because "(t)he disclosure has not shown (i) which portions of SEQ ID NO:9 are critical to the activity of the protein of SEQ ID NO:10; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO:9 (*sic*; that) will result in protein mutants with the same functions as the protein of SEQ ID NO:10" (the Action at page 4). Applicants point out that the above comment is **completely irrelevant** to determining whether the claimed compositions meet the legal requirements for patentability under 35 U.S.C. § 112, first paragraph. There is absolutely **no** requirement that all species of an invention must have all of the exact same properties, or, more specifically, that novel nucleotide fragments of SEQ ID NO:9 must have the exact same function as the full length sequence of SEQ ID NO:9, or encode polypeptides that have the exact same function as the full length amino acid sequence of SEQ ID NO:10, in order to meet the enablement requirement under 35 U.S.C. § 112, first paragraph. It is well established that the enablement requirement is met if **any** use of the invention (or in this case, certain species of the invention) is provided (*In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1985)). ""The enablement requirement is met if the description enables any mode of making and using the invention" (*Johns Hopkins Univ. v. CellPro, Inc.*, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991)). Enablement only requires that the specification describe

a practical use for the composition defined in the claims, and that a skilled artisan be able to make and use the claimed DNA segments without undue experimentation. Accordingly, the presently claimed invention clearly meets the enablement requirement under 35 U.S.C. § 112, first paragraph.

The Action seems to contend that the specification provides insufficient guidance regarding the biological function or activity of certain of the claimed compositions. However, such an enablement standard conflicts with established patent law. As discussed in *In re Brana,* 34 USPQ2d 1436 (Fed. Cir. 1995; "*Brana*"), the Federal Circuit admonished the United States Patent and Trademark Office ("the USPTO") for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption" (*Brana* at 1442).

The Examiner cites *In re Wands* (8 USPQ 2d 1400 (Fed. Cir. 1988); "*Wands*") as defining "(t)he factors that are considered when determining whether a disclosure satisfies (*sic*; the) enablement requirement", which "include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims" (the Action at page 4). Applicants are well aware of the "Wands factors" that are to be considered in determining enablement of claims, but respectfully point out for the record that after properly setting forth these factors, the Action in fact does not provide any reasoned consideration of these factors with regard to the breadth of the presently claimed invention. Rather, the Action focuses on a single aspect of the present invention, namely, the biological function of the full length protein encoded by the full length nucleotide sequence of SEQ ID NO:9, before concluding that "it would require undue experimentation for one skilled in the art to make and use the claimed genus of nucleic acid molecules embraced by the instant claim" (the Action at page 5). Applicants respectfully point out that such conclusory statements are not sufficient to support the present rejection, and therefore provide an analysis of each of the "Wands factors" with regard to the breadth of the present invention.

First, with regard to "the quantity of experimentation necessary", Applicants point out that significant commercial exploitation of nucleic acid sequences, such as the presently claimed sequences, requires no more information than the nucleic acid sequence itself. As the nucleic acid sequence of

SEQ ID NO:9 is clearly disclosed in the specification as originally filed, such commercial exploitation requires **no** experimentation. As SEQ ID NO:9, the nucleotide sequence encoding SEQ ID NO:10, has been found by the USPTO to have a specific, substantial, and credible utility (see U.S. Patent No. 6,777,232), and as isolated nucleic acid molecules comprising at least 80 contiguous bases of nucleotide sequence from SEQ ID NO:9 have been found to be novel (as there are no art rejections under 35 U.S.C. §§ 102 or 103 set forth in the Action), **all** of the presently claimed nucleic acid molecules are unique identifiers of SEQ ID NO:9. Thus, applications ranging from gene expression analysis or profiling (utilizing, for example, arrays of overlapping or non-overlapping oligonucleotides and DNA chips) to chromosomal mapping and genomic cloning (utilizing, for example, oligonucleotide probes) can be practiced by the skilled artisan utilizing the presently claimed nucleic acid sequences with no experimentation at all - the skilled artisan merely selects a nucleic acid molecule comprising at least 80 contiguous bases of nucleotide sequence from SEQ ID NO:9, in conjunction with techniques that are well-known in the art. Thus, the presently claimed invention clearly meets the enablement requirement under the first "Wands factor".

With regard to "the amount of direction or guidance presented", Applicants respectfully point out that there is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further directions or guidance in the present specification, as detailed above. For example, it is not unreasonable to expect a Ph.D. level molecular biologist to be able to use the disclosed sequence to design oligonucleotide probes and primers and use them in, for example, PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Nevertheless, the present specification provides significant direction and guidance to the skilled artisan by providing highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed invention, including recombinant expression, site-specific mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques. Additionally, the specification as originally filed properly incorporates by reference a montage of standard texts into the specification, such as "Molecular Cloning, A Laboratory Manual" (Sambrook *et al.*, eds. Cold Spring Harbor Press, Cold Spring Harbor, NY, 1989) and "Current Protocols in Molecular Biology" (Ausubel *et al.*, eds. Green Publishing Associates, Inc., and John Wiley & Sons, Inc., New York, NY, 1989), to provide

even further guidance to the skilled artisan. Such incorporation of material into the specification by reference is proper (*Ex parte Schwarze*, 151 USPQ 426 (PTO Bd. App. 1966)). In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra.* In fact, it is preferable that what is well-known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As standard molecular biological techniques are routine in the art, such protocols do not need to described in detail in the specification. Thus, the presently claimed invention clearly meets the enablement requirement under the second "Wands factor".

With regard to "the existence of working examples", Applicants acknowledge that there are no working examples in the specification as originally filed. However, it has long been established that "there is no statutory requirement for the disclosure of a specific example" (*In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA, 1962)). Further, as the "nature of the invention" (the fourth "Wands factor") concerns isolated nucleic acid sequences, which have been employed for decades in a wide variety of applications, specific working examples are hardly required for the skilled artisans to "make and use" the claimed invention, as detailed above. The fact that skilled artisans have been making and using isolated nucleic acid sequences for decades, along with the widespread commercial exploitation of nucleic acid sequence information (as detailed above), and fact that standard texts on such subjects as molecular biology, protein expression and isolation, and antibody production and utilization have been in widespread circulation throughout the scientific community for over a decade prior to the filing of the present application, all point to "the state of the prior art" (the fifth "Wands factor"), and "the relative skill of those in the art" (the sixth "Wands factor"), the presently claimed invention clearly meets the enablement requirement under the fourth, fifth, and sixth "Wands factor".

With regard to "the predictability or unpredictability of the art" (the seventh "Wands factor"), Applicants submit that with regard to a large number of different applications utilizing the claimed nucleic acid sequences, the predictability of the art is quite high. As detailed above, applications such as gene expression analysis or profiling, chromosomal mapping and genomic cloning, PCR, recombinant expression, random and site-specific mutagenesis, *in situ* hybridization, large scale nucleic acid

screening techniques, and antibody (both polyclonal and monoclonal) production and screening, have been practiced for years, and in some cases decades, by the skilled artisan. In fact, such techniques and applications have become routine and commonplace, precisely because they **are** predictable. The Action cites Ngo *et al.* ("The Protein Folding Problem and Tertiary Structure Prediction" (Merz, ed., Birkhauser, Boston, MA, 1994) for the proposition that "the relationship between sequence of a protein and its activity is not well understood and is not predictable" (the Action bridging pages 4 and 5). While the relevance of a 10 year old reference to the state of the art at the time of filing of the present application is questionable at best, this argument is again **completely** misplaced, because, as detailed above, there is absolutely **no** requirement that all species of an invention must have all of the exact same properties, or, more specifically, that novel nucleotide fragments of SEQ ID NO:9 must have the exact same function as the full length sequence of SEQ ID NO:9, or encode polypeptides that have the exact same function as the full length amino acid sequence of SEQ ID NO:10, in order to meet the enablement requirement under 35 U.S.C. § 112, first paragraph. Thus, given the overall predictability of the relevant art, the presently claimed invention clearly meets the enablement requirement under the seventh "Wands factor".

Finally, with regard to "the breadth of the claims" (the eighth "Wands factor"), Applicants respectfully point out that all of the species encompassed in the present claims can be utilized in most, if not all, of the applications described above, including gene expression analysis or profiling, chromosomal mapping and genomic cloning, PCR, recombinant expression, random and site-specific mutagenesis, *in situ* hybridization, large scale nucleic acid screening techniques, and antibody (both polyclonal and monoclonal) production and screening. Thus, although somewhat broad, the presently claimed invention clearly meets the enablement requirement under the eighth "Wands factor".

Therefore, as the presently claimed invention meets seven of the eight "Wands factors", Applicants submit that the present rejection under 35 U.S.C. § 112, first paragraph, is *prima facie* improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements

contained therein which must be relied on for enabling support.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971), emphasis as in original.

Additionally, with regard to the allegation in the Action that "it would require undue experimentation for one skilled in the art to make and use the claimed genus of nucleic acid molecules embraced by the instant claim", it is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation" (*In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976)). In *Wands* (*supra*), the USPTO took the position that the applicant failed to demonstrate that the disclosed biological processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the rejection set forth by the USPTO, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

Finally, Applicants point out that a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it" (*In re Naquin*, 158 USPQ

317, 319 (CCPA 1968); emphasis added). The present claims are thus enabled as they are supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed.

As detailed above, all aspects of the enablement rejection under 35 U.S.C. § 112, first paragraph have been overcome. Applicants therefore respectfully request that the rejection be withdrawn.

IV. Rejection of Claims 1, 7 and 8 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1, 7 and 8 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

The Action states that claims 1, 7 and 8 fail to meet the written description requirement because "(t)he instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of nucleic acid molecules" (the Action at page 6). However, the Action **admits** that claims 1, 7 and 8 in fact do include a "definitive structural feature of the claimed genus of nucleic acid molecules", specifically, that the nucleic acid molecule must include "a stretch of at least 80 consecutive nucleotides that is the same as SEQ ID NO:9" (the Action at page 5). Applicants respectfully point out that this is **all that is required** of claims 1, 7 and 8 to meet the written description requirement of 35 U.S.C. § 112, first paragraph. The Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

In claims involving chemical materials, generic formulae usually indicate with specificity

> what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function (as seemingly required by the Action), or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

The Action actually cites *Univ. of California v. Eli Lilly and Co.* for the proposition that "(a) description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, **or of a recitation of structural features common to the genus**" (the Action at page 6). Applicants reiterate that the structural feature that is common to the **entire claimed genus** is "at least 80 contiguous bases of nucleotide sequence from SEQ ID NO:9", exactly as set forth in claim 1. Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific **structural** description provided. Polynucleotides comprising at least 80 contiguous bases of nucleotide sequence first disclosed in SEQ ID NO:9 are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1, 7 and 8 thus meet the written description requirement.

Finally, the Action states that claims 1, 7 and 8 fail to meet the written description requirement because "there is no information regarding the relation of structure to function" (the Action at page 6). Applicants respectfully point out that this comment is **completely irrelevant** to determining whether the claimed compositions meet the legal written description requirements for patentability under 35 U.S.C. § 112, first paragraph. As set forth above, an adequate description of a genus merely "requires a precise definition, such as by structure, formula, chemical name **or** physical properties" sufficient to distinguish the genus from other materials (*Fiers, supra*, emphasis added). In other words, structure **or** function is required, not structure **and** function. As a precise definition of the structure and formula of the claimed genus sufficient to distinguish the genus from other materials is in fact provided in the present case, specifically, that the members of the genus comprise "a stretch of at least 80 consecutive nucleotides that is the same as SEQ ID NO:9", the claimed invention in clearly in compliance with the written description requirement under 35 U.S.C. § 112, first paragraph.

Applicants therefore respectfully request that the rejection of claims 1, 7 and 8 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Li have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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